Remarks/Argument

Substitute Specification

The specification has been amended to correct spelling errors by substituting the word "self-microemulsifiable" for "self-microemulsifyable" and substituting the word "performed" for "preformed". A clean version of the specification, excluding the claims, is submitted with this Reply that incorporates the amendments disclosed above. The substitute specification includes no new matter.

Information Disclosure Statement

In response to the examiner's objection to the information disclosure statements filed on August 4, 2006, November 9, 2009, and June 7, 2010, applicants filed additional information disclosure statement on August 31, 2010, which included the submission of copies of all cited foreign patent documents.

Pending Claims

Claims 74 – 79, 84 – 86, and 89 – 93 remain in this application. Claims 87 and 88 have been canceled. Claims 80 – 83, 94 – 109 have been withdrawn without prejudice.

Claim Objections

The examiner's objections to claims 74-79 and 84-93 are acknowledged and corrections are submitted with the amended claims.

Summary of Claim Amendments

Claim 74 has been amended: to substitute the word "self-microemulsifiable" for "self-microemulsifyable"; to add that the base composition is for use in the preparation of "a spontaneously formed and thermodynamically stable microemulsion" (specification at page 3, line 18 - page 4 line 2 (substitute specification at paragraph [0005]); specification at page 7, lines 8-9 (substitute specification at paragraph [0009]); specification at page 14 lines 14-16 (substitute specification at paragraph [0020]); and

specification at page 15, lines 11-21 (substitute specification at paragraph [0022])); to add that propofol is "liquid propofol" (specification at page 8, lines 8-14 (substitute specification at paragraph [0011]); and specification at page 19, line 20 - page 20, line 8 (substitute specification at paragraph [0031])); to clarify that the "POE" is "polyoxyethylene" and that the "PEG" should be "POE" ; and to clarify that the claim does not contain any other surfactant other than the claimed nonionic surfactant having the claimed structure.

Claim 84 has been amended: to substitute the word "self-microemulsifiable" for "self-microemulsifyable"; to add a disclosure that the base composition is for use in the preparation of "a spontaneously formed and thermodynamically stable microemulsion" (specification at page 3, line 18 - page 4 line 2 (substitute specification at paragraph [0005])); specification at page 7, lines 8-9 (substitute specification at paragraph [0009]); specification at page 14 lines 14-16 (substitute specification at paragraph [0020])); and specification at page 15, lines 11-21 (substitute specification at paragraph [0022])); to add that propofol is "liquid propofol" (specification at page 8, lines 8-14 (substitute specification at paragraph [0011])); and specification at page 19, line 20 - page 20, line 8 (substitute specification at paragraph [0031])); to clarify that the "POE" is "polyoxyethylene" and that the "PEG" should be "POE"; to clarify that the claim does not contain any other surfactant other than the claimed nonionic surfactant having the claimed structure; and to incorporate the limitations of dependent claims 87 and 88 that have been canceled.

Withdrawn claims 108 and 109 have been amended to substitute the word "self-microemulsifiable" for "self-microemulsifyable".

Claim Rejections: 35 USC § 102

The Examiner submits that claims 74-76 and 78-79 are anticipated by Dennis et al. (US Patent No. 6,638,537; hereinafter "*Dennis*"). Applicants respectfully disagree.

Dennis

Dennis discloses a "microemulsion delivery system for insoluble or sparingly water soluble drugs that comprises a long polymer chain surfactant component and a short-chain fatty acid surfactant component with the amount of each surfactant being selected to provide stable microemulsion or micellar systems" (Abstract). More specifically, *Dennis* discloses a microemulsion delivery system for propofol that has an "appropriate combination of surfactants" with one surfactant being a "long chain polymer surfactant component such as a poloxamer" and with another surfactant being a "short chain fatty acid surfactant component" (column 7, lines 57-61). Contrary to the disclosure in *Dennis*, applicants' amended claim 74 is specifically limited to a self-microemulsifiable anhydrous base composition containing a nonionic surfactant, with the base composition not containing any other surfactant other than said nonionic surfactant having the chemical structure recited in the claim. In this regard, to the extent that the examiner contends that original claim 74 did not exclude a nonionic surfactant and an anionic surfactant, claim 74 has been amended to exclude any other "surfactant" other than said nonionic surfactant. Accordingly, applicants respectfully submit that *Dennis* does not anticipate the amended claims.

Although applicants submit that the two component surfactant formulation disclosed in *Dennis* clearly establishes that *Dennis* does not anticipate the amended claims, applicants also respond to the examiner's additional arguments. The examiner contends that *Dennis* discloses a "self-microemulsifiable" composition as in claim 74. The examiner reaches this conclusion based upon the disclosure in *Dennis* set forth in claim 1 that the surfactant and co-surfactant are selected to provide for spontaneous formation of a thermodynamically stable microemulsion. Applicants respectfully disagree with this conclusion. *Dennis* discloses and claims a microemulsion that contains an "aqueous phase". The instant application claims a "self-microemulsifiable anhydrous base composition", which specifically excludes an aqueous phase.

The examiner also argues, however, that *Dennis* further discloses that " [i]n order to make a homogenous microemulsion of ... propofol, one needs to mix it with the appropriate emulsifier combination for formation of the microemulsion" (column 7, lines 49-56). Since this disclosure in *Dennis* also does not expressly describe the formation

of a self-microemulsifiable anhydrous base composition, applicants assume that the examiner is of the opinion that the reference *implicitly or inherently* discloses the existence of a self-microemulsifiable base, because propofol may be mixed with the emulsifier combination before adding saline to form the aqueous phase (column 10 line 65 through column 11 line 5; and Table 1). It is well established, however, that the "fact that a certain result or characteristic *may* occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic". MPEP § 2112 (emphasis in original). Since the microemulsion containing propofol could be formed by adding the components in any order or even simultaneously and since *Dennis* does not disclose that one order is preferable to any other order, there is no basis in fact or law to conclude that the order is as contended for by the examiner.

Based upon the foregoing, applicants submit that *Dennis* does not anticipate claims 74-76 and 78-79. Accordingly, applicants respectfully request withdrawal of this rejection and allowance of the pending claims.

Claim Rejections: 35 USC § 103

1) Claims 74 – 76 and 78 – 79:

The examiner further contends that, even if *Dennis* does not anticipate the specific combination of propofol and a nonionic surfactant having the structure recited in claim 74, the claim is *prima facie* obvious because the nonionic surfactant Tween 20 is suggested by the reference as a suitable nonionic surfactant. Without admitting that the examiner's contention regarding Tween 20 is correct, the claim is not obvious over *Dennis*, because the reference does not teach the limitation of amended claim 74 of a nonionic surfactant within a self-microemulsifiable anhydrous base composition that does not contain any other surfactant other than said nonionic surfactant having the claimed structure. Rather, *Dennis* expressly teaches, as set forth above, that in order to form a microemulsion containing propofol the aqueous composition must include a long polymer chain surfactant component and a short-chain fatty acid surfactant component surfactant. There is no suggestion in *Dennis* that a single surfactant component could

be used to form microemulsions containing propofol. Accordingly, applicants respectfully request withdrawal of this rejection and allowance of the pending claims.

2) Claims 74, 77 and 84 – 93:

Next, the examiner argues that claims 74, 77 and 84 – 93 are unpatentable over *Dennis* in view of Pace et al. (US Patent No. 6,726,537; hereinafter "*Pace*"). Again, applicants respectfully disagree.

The examiner recognizes that claim 84 is not anticipated by *Dennis* due to the additional claim limitation of a water-immiscible solvent. However, the examiner contends that it would have been obvious to have used a water-immiscible solvent, like ethyl oleate, in the formulation of *Dennis*, because a person having ordinary skill in the art would have been motivated by the desire to use a solvent that can dissolve propofol at all temperatures as disclosed by *Pace*. Before addressing this contention, applicants submit that *Pace* is not analogous prior art for use in an obviousness analysis.

Scope of the Prior Art

Two criteria are relevant in determining whether prior art is analogous: (1) whether the art is from the same field of endeavor, regardless of the problem addressed; and (2) if the reference is not within the field of the inventor's endeavor, whether the reference is still reasonably pertinent to the particular problem with which the inventor is involved. *In re Clay*, 966 F.2d 656 (Fed. Cir. 1992); and *In re ICON Health and Fitness, Inc.*, 496 F.3d 1374 (Fed. Cir. 2007). The *In re ICON* decision addressed the issue of analogous prior art after the Supreme Court's holding in *KSR International Co. v. Teleflex, Inc.*, 127 S. Ct. 1727 (2007) and held that the second analogous art criteria that the reference must be "reasonably pertinent to the problem with which the inventor is involved" was equivalent to the statement in *KSR* that "familiar items may have obvious uses beyond their primary purposes".

Although applicants agree that *Dennis*, which is directed to thermodynamically stable microemulsion or micellar systems, is from the same field of endeavor as the claimed self-microemulsifiable anhydrous base composition for use in the preparation of a microemulsion, applicants do not agree that *Pace* is from that field of endeavor.

Pace is not directed to a spontaneously formed and thermodynamically stable microemulsion as described in amended claims 74 and 84. Rather, the reference is directed to an exceeding small category of formulations that are referred to in the prior art as microdroplets (column 3, lines 39-53; and column 12, lines 39-42). In this regard, it appears that the first disclosure of microdroplets is found in a patent issued to Duncan H. Haynes in 1986 (U.S. Pat. No. 4,622,219) and later described by the same inventor in a patent issued in 1997 (U.S. Pat. No. 5,637,625). In the first Haynes patent, the inventor describes his formulation as having the novel feature of using volatile liquid general anesthetics to produce local anesthesia (column 1, lines 39-43). The microdroplet formulation is described as comprising a center containing the water-insoluble/organic phase containing the drug substance, surrounded by an outer unimolecular layer of lipid, such as lecithin (column 3, lines 7-12). And, the formulation is prepared by reducing the water-insoluble oil or anesthetic phase to microscopic dimensions by the use of sonication, and then coating the resulting structure with a layer of a lipid (column 3, lines 27-31). In this regard, the utilization of external energy (i.e. sonication) to form the microdroplet formulation would teach a person having ordinary skill in the art that the resulting lecithin-coated microdroplet formulation is only temporarily stable and that the formulation will tend to coalesce over time, resulting in a collapse of the formulation. In fact, the reference explicitly confirms that the formulation is only temporarily stable by disclosing that the formulation is "stable for several days" at 30°C (column 8, lines 45-46). Additionally, the reference discloses that the formulation is "slightly cloudy to the eye" (column 8, lines 38-39). The second Haynes patent, specifically mentioned in *Pace*, describes a microdroplet formulation that is similar to the formulation of the first Haynes patent, but with propofol used as the drug substance. The reference describes the formulation as comprising "lecithin-coated propofol microdroplets" in a "homogenous off-white suspension" (column 3, lines 59-61). Similarly, the "preparation of the propofol microdroplets requires an intense mechanical agitation or high sheer", with the preferred method being sonication (column 3, lines 3-4). Again, this manner of preparation would suggest to a person having ordinary skill in the art that the propofol microdroplets are only temporarily stable.

Applicants submit that it should be undisputed that the above-described Haynes patents relate to the formation of classic emulsions, not microemulsions. It is well known to persons having ordinary skill in the art that an emulsion is a mixture of two or more immiscible liquids that is initially formed by applying an external energy to the mixture in order to form a dispersed and a continuous phase solution, with the dispersed phase comprising droplets of, for example, oil in an oil-in-water type of emulsion. In general, the external energy used to form the emulsion is generated from procedures like homogenization, sonication, or microfluidization. Typically, a surfactant is also used in order to temporarily stabilize the emulsion against coalescence, with the surfactant forming a protective layer between the oil droplets and the aqueous phase. This description of an emulsion is precisely the type of solution that is described in the Haynes patents. Both Haynes patents describe the formation of the microdroplets by mixing a drug phase in an aqueous phase, with the addition of a surfactant in order to temporarily stabilize the drug core against coalescence, and subjecting the mixture to sonication in order to form the emulsion, which the Haynes inventors call a "microdroplet formulation". Evidently, the inventors coined this phrase due to the relatively small droplet sizes that are formed by using intense mechanical agitation or high sheer.

Now, returning to *Pace*, the reference describes a microdroplet formulation containing propofol microdroplets or micromatrices that are suspended in an aqueous medium (column 12, lines 41-42). The micromatrices or microdroplets are disclosed as being water-insoluble and comprise one or more propofol-soluble diluents (column 13, lines 9-11). The diluents can be dissolved in the propofol as a liquid or as a solid or as a slush (column 13, lines 11-13). When the composition inside the micromatrix is completely liquefied, each micromatrix particle is a microdroplet (column 13, lines 21-22). In one embodiment, *Pace* discloses that the propofol-soluble diluent can dissolve in propofol at all temperatures (column 13, lines 35-36). In other embodiments, the propofol diluent can dissolve in propofol at temperatures above room temperature (column 13, lines 36-49). Apparently, the diluent is selected such that when dissolved in propofol the composition has a melting pointing point above room temperature but below body temperature (Id). The inventors claim that when this formulation is injected

into the body, the propofol is in a solid or semi-solid state within the diluent and, as a result, does not interact with the surface of the skin to cause pain on injection (column 13, lines 49-67). When the formulation enters the blood stream, however, the solid or semi-solid containing the propofol dissolves, releasing the drug for absorption within the body (Id). The microdroplet formulation is prepared by separately forming an aqueous phase and a lipophilic phase, which are then premixed to form a suspension, which is then subjected to external energy in the form of microfluidization (column 24, lines 62-67). The patent states that at the surface of the water-insoluble micromatrices or microdroplets or otherwise at the micromatrix-water interface or microdroplet-water interface there is a surface stabilizing amphiphilic agent that "stabilizes the micromatrix or microdroplet dispersion against coalescence and against microemulsion collapse" (column 15, lines 7-18). In one embodiment, the patent discloses that the aqueous phase of the formulation may additionally contain an amount of a pH adjusting agent in an amount that "does not cause the *emulsion* to collapse (column 16, lines 54-60; emphasis supplied).

Based upon this description of the microdroplet formulation in *Pace*, it should be undisputed that the formulation is an *emulsion* that is formed by applying a form of external energy to the components making up the formulation, just like the emulsions described in the Haynes patents. In fact, *Pace* occasionally refers to the propofol microdroplet formulation as an emulsion (column 16, lines 54-60 [quoted above]; and column 17, lines 56-61 [the formulation can provide increased patient safety during "repeated use from the same vial of "propofol *emulsion* of this invention" (emphasis supplied)]). Although *Pace* also refers to the surface stabilizing amphiphilic agent as stabilizing the dispersion against "microemulsion collapse", it should be clear from the foregoing that the inventors are not referring to the collapse of a microemulsion, but to the collapse of the micromatrix or microdroplets. Further, the use of the phrase is a misnomer because, as is known to persons skilled in the art, once a microemulsion is formed, it will remain thermodynamically stable indefinitely. In this regard, neither *Pace* nor the Haynes patents claim that their formulations are or could be formed spontaneously without the use of external energy, or that their formulations are thermodynamically stable. Rather, all of the references require the use of an external

energy source, such as sonication or microfluidization, to form the microdroplets. The only other reference made in *Pace* to a microemulsion is the following statement: the "compositions" of the invention are "stable as microemulsions in the presence of the antimicrobial agent for at least six months ... and most preferably for at least two years" (column 12 lines 58-column 13 line 2). However, when this statement is read in context, it is again apparent that the statement is not meant to claim that the "composition" of the invention is a microemulsion. What the statement obviously means is that the composition will have *stability against microbial contamination* for up to the specified times. The statement cannot be reasonably read to suggest that the composition is a microemulsion that is a spontaneously formed and thermodynamically stable solution as in the present invention. Furthermore, the utilization of microfluidization to form the microdroplet formulation would teach a person having ordinary skill in the art that the formulation is only temporarily stable and will tend to coalesce over time, resulting in a collapse of the formulation.

Since the *Pace* reference relates to the field of chemical *emulsions* containing propofol, applicants submit that it is not analogous art because the claimed invention relates to the field of chemical *microemulsions*, and more specifically relates to the field of self-microemulsifiable base compositions that can be used in the preparation of a spontaneously formed and thermodynamically stable microemulsion containing propofol. Although there may appear to be some superficial similarity between emulsions and microemulsions due to the similarity of their names, the chemistry and thermodynamics involved in the formation of emulsions and microemulsions have almost no similarities. As discussed above, emulsions are formed by mixing two or more immiscible liquids and then by applying an external energy, like sonication or microfluidization, to the mixture in order to form a dispersed phase and a continuous phase emulsion. Optionally, a surfactant can be used to provide some limited stability to the emulsion by inhibiting coalescence. More specifically, in an emulsion of propofol as described, for example, in the Haynes and *Pace* patents, the surfactant forms a protective layer or coating around the propofol droplets at the interface between the droplets and the aqueous medium within the dispersed phase of the emulsion.

The chemistry and thermodynamics involved in the formation of the microemulsion of the claimed invention, which is formed spontaneously when the self-microemulsifiable base composition of amended claim 84 is simply mixed with or added to the physiologic carrier solution, is completely different. When the carrier liquid is added to the claimed solution containing liquid propofol, a nonionic surfactant, a water-immiscible solvent, and ethanol, the surfactant forms a microemulsion or micellar solution *spontaneously*, with the microemulsion forming without the use of any externally applied energy to drive the formation. The spontaneously formed microemulsion or micellar solution consists of spherically shaped micelles that, in turn, consist of aggregates of surfactant molecules with the hydrophilic end of each molecule being chemically attracted to the carrier liquid and the hydrophobic end of each molecule being chemically attracted to the liquid propofol (specification at page 14, lines 7-17 (substitute specification at paragraph [0020]); and specification at page 18, line 18 – page 19, line 12 (substitute specification at paragraph [0029])). The hydrophilic ends of the surfactant molecules extend outward into the aqueous solution and the hydrophobic ends of the surfactant molecules extend into the center of the micelle and form a jumbled assemblage of hydrophobic ends that contains the propofol and water-immiscible solvent dispersed within the assemblage, essentially forming a single phase of propofol molecules disposed *within* the surfactant molecules (specification at page 18, line 18 – page 19, line 12 (substitute specification at [0029])). In the emulsion of propofol as described, for example, in the Haynes and *Pace* patents, the surfactant forms a protective layer or coating around the propofol droplets at the interface between the droplets and the aqueous medium, thereby forming a two phase formulation of surfactant *surrounding* the propofol droplets.

In addition to forming spontaneously, the microemulsion that is formed by using the base composition of the present invention is thermodynamically stable (specification at page 9, lines 7 – 9 (substitute specification at paragraph [0012]); and specification at page 21, lines 2 – 4 (substitute specification at paragraph [0032])). The microemulsion is thermodynamically stable due to the fact that the process of microemulsion formation is driven solely by the chemical interactions of the compositions within the solution, without the utilization of an external energy (e.g. sonication or microfluidization), as

required by the Haynes and *Pace* references. Further, as is known to those skilled in the art, "thermodynamically stable" means that the microemulsion is stable indefinitely because no external energy is used in its formation. The microdroplet formulations of Haynes and *Pace*, on the other hand, are only temporarily stable (i.e. kinetically stable) since energy is required to form the emulsion. Over time, as the energy of the emulsion begins to dissipate due to the interaction of the oil phase droplets, the droplets will begin to coalesce, leading to emulsion collapse.

The microemulsion of the present invention is also optically transparent, which as is known to persons skilled in the art is another characteristic of a microemulsion. On the other hand, the emulsions described in the Haynes references are not optically transparent, but are cloudy and off-white. *Pace* does not disclose the optical characteristics of its microdroplet formulation, but since *Pace* discloses microdroplet formulations as first disclosed in the Haynes references, it must be assumed that the microdroplets described in *Pace* are also cloudy or off-white.

Accordingly, based upon the significant chemical and thermodynamic differences between an emulsion and the self-microemulsifiable base composition for use in the preparation of a spontaneously formed and thermodynamically stable microemulsion of the claimed invention, applicants contend that the *Pace* reference is not from the same field of endeavor as that related to the claimed invention.

Further, applicants contend that *Pace* is not reasonably pertinent to the particular problem being addressed by applicants. As stated in the instant application, the problem that applicants have addressed is to provide a high concentration of propofol in a self-microemulsifiable base composition that can be used to prepare a microemulsion for intravenous injection after mixing the base with a carrier liquid (specification at page 6, line 21 – page 7, line 8 (substitute specification at paragraph [0009])). It should be apparent from the above discussion regarding the fields of endeavor that *Pace* is not related to the formation of a self-microemulsifiable base composition for use in the preparation of a microemulsion. Rather, *Pace* is principally related to the problems of providing an emulsion containing propofol that allegedly overcomes limitations in the prior art disclosed in the Haynes patents relating to pain at the site of injection and an increase in hyperlipidemia due to prolonged use of a

formulation containing large quantities of vegetable oil (column 2, line 39 – column 3, line 58). None of these problems ostensibly addressed by *Pace* were of concern to the applicants.

Accordingly, applicants contend that *Pace* is not reasonably pertinent to the particular problem with which the present inventors are involved. Therefore, applicants respectfully submit the *Pace* reference is not analogous art that can be reasonably relied on in support of the obviousness objection.

Dennis in view of Pace

Assuming, without admitting, that the *Pace* reference discloses analogous art, applicants disagree with the examiner's conclusion that the claims are obvious over *Dennis* in view of *Pace*. The examiner has rejected the claims based upon the allegation that it would have been obvious to have used a water-immiscible solvent, like ethyl oleate, in the formulation of *Dennis*, because a person skilled in the art would have been motivated by the desire to use a solvent that can dissolve propofol at all temperatures as disclosed by *Pace*. On the contrary, a person having ordinary skill in the art would not have been motivated to dissolve propofol in the formulation of the claimed base composition, because the propofol that is used in the formulation is already in liquid form at room temperature (specification at page 8, lines 8 -14 (substitute specification at paragraph [0011]); specification at page 19, line 20 - page 20, line 8 (substitute specification at paragraph [0031]); and original claim 84 has been amended to claim that the base composition contains "liquid propofol"). Similarly, since *Dennis* also discloses that propofol is in liquid form at room temperature, the reference does not suggest or teach the need to utilize a water-immiscible solvent, like ethyl oleate, to dissolve propofol (column 2, lines 42-44). In this regard, *KSR International Co. v. Teleflex, Inc.*, *supra.*, holds that "any need or problem known in the field of endeavor at the time of the invention and addressed by the patent [or patent application] can provide a reason for combining the elements in the manner claimed". This holding is expressly limited to the "field of endeavor" and to subject matter "addressed by the patent" or, as in the instant case, addressed by applicants. As argued above, the field of self-microemulsifiable base compositions and microemulsions addressed by

applicants is clearly not reasonably related to the field of emulsions addressed by *Pace*. And, even if the two fields were related, the instant application does not expressly or implicitly address the problem of dissolving propofol. Rather, as disclosed in the application, the water-immiscible solvent is added to the base composition in order to increase the concentration of propofol within the microemulsion to levels much higher than is possible by using the formulation of amended claim 74 to form the microemulsion that does *not* utilize a water-immiscible solvent (specification at page 22, lines 1-6 (substitute specification at paragraph [0034])).

Accordingly, applicants submit that a person having ordinary skill in the art would not have been motivated to look to *Pace*, or to any other reference, for a chemical substance that could have been used to address the problem of dissolving propofol, because the liquid propofol that is disclosed and claimed in the present application obviously does not need to be dissolved. Further, due to the substantial differences in the chemistry and thermodynamics between an emulsion and a microemulsion, applicants submit that a person having ordinary skill in the art would not have been able to predict, without extensive experimentation, whether ethyl oleate would have been useful in the formation of a microemulsion from the claimed self-microemulsifiable base composition in which ethyl oleate is combined with liquid propofol, a single nonionic surfactant having the claimed formula, and ethanol; and more specifically, whether the inclusion of ethyl oleate in the base composition would have allowed an increase in the concentration of propofol in the resulting microemulsion to levels substantially higher than was attainable without the use of the water-immiscible solvent in the base and without increasing concentrations of the nonionic surfactant in the base. In fact, the present inventors have discovered that the concentrations of nonionic surfactant in the base composition can actually be *decreased* when the claimed concentrations of ethyl oleate are used in the base: a discovery that contradicts the prevailing understanding of those skilled in the art that additional surfactant would have to be included in the base composition in order to solubilize the added water-immiscible solvent when a carrier liquid is added to the base in order to form the microemulsion.

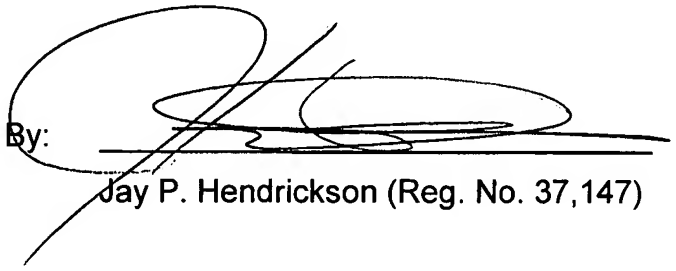
Equally important is the fact that *Pace*, alone or in combination with *Dennis*, does not disclose or teach the formation of a self-microemulsifiable base composition for use

in the preparation of a spontaneously formed and thermodynamically stable microemulsion containing propofol. As discussed above, *Pace* discloses the formation of microdroplets or micromatrices that are formed by combining propofol, a propofol-soluble diluent, a surface stabilizing amphiphilic agent, an antimicrobial agent, and an excipient, and then subjecting the mixture to microfluidization in order to form the microdroplets or micromatrices. The reference discloses that the amphiphilic agent covers the surface of a microdroplet core containing the propofol and the propofol-soluble diluent. Again, this formulation is an emulsion, not a microemulsion. There is no suggestion in *Pace* to the effect that its formulation is or could be formed spontaneously without subjecting the mixture to intense agitation or high sheer, or that the formulation is or could be thermodynamically stable. Similarly, there is no suggestion in *Pace* in combination with *Dennis* that would indicate to a person having ordinary skill in the art how the microdroplets in *Pace* could be converted to the microemulsions disclosed in *Dennis*.

Finally, the examiner's obviousness rejection cannot be supported in view of the additional amendments to original claim 84. The amended claim now provides, among other things, that the relative concentration of the nonionic surfactant to propofol in the self-microemulsifiable base composition is not less than three (3) parts of nonionic surfactant to about one (1) part of propofol, which translates to a ratio of propofol to surfactant of not more than about 0.3. *Pace*, on the other hand, discloses and claims a ratio of the propofol to the amphiphilic agent to be in the range of from about 0.4 to about 1.5. As a result, *Pace* discloses ratios of propofol to surfactant that do not include the ratio of propofol to surfactant in amended claim 84. And, there is nothing in *Pace* to suggest that, under some circumstances, the ratio of propofol to surfactant can be decreased so as to include the claimed ratio and still form microdroplets or micromatrices. Although a *prima facie* case of obviousness might exist where the claimed ranges and prior art do not overlap, it must be shown that a person skilled in the art would have expected the compositions to have the same properties (M.P.E.P. §2144.05). Certainly, in this case such a showing is not possible due to the fact that *Pace* discloses an emulsion, rather than a microemulsion.

Thus, applicants respectfully request that this rejection be withdrawn, that all pending claims be allowed, and that all withdrawn claims be considered for allowance.

Respectfully submitted,



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